Dose-Response Modeling for Assessing Cumulative Pesticide Risk

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ETD Peer Review — Experimental Toxicology Division — N H E E R L

A. Dose-Response Modeling for the Organophosphate Cumulative Risk Assessment

ENVIRONMENTAL ISSUE: While most dose-response methodologies have been developed for exposures to single agents, real-world exposures are generally to multiple agents, often operating through the same mode of action. In recognition of this, the Food Quality Protection Act (FQPA) requires the Agency to consider cumulative exposures to agents that act through a common mode of action when it sets tolerances for pesticides. Dose-response analysis in this setting requires assessing the consequences of exposure to a continuously varying mixture of pesticides in food, drinking water, and through dermal or inhalation exposure. Single-component approaches, in which the consequences of exposure to the mixture is predicted by combining the results of individual dose-response models, allow

STUDY GOALS: The long-term goal of this work is to develop improved mathematical and statistical methodologies for evaluating and incorporating dose-response information into risk assessments for cumulative exposure to environmental toxicants, particularly pesticides.

Specific Subprojects:

A. Develop empirical dose-response models and statistical methods for fitting them to data for calculating relative potency factors (RPFs) and their confidence intervals for a set of 33 organophosphate (OP) pesticides, for EPA's Cumulative Risk Assessment for those pesticides.

B. Develop PBPK/PD models for exposure to multiple n-methyl carbamate pesticides, along with empirical dose-response models, compare their risk predictions, and develop methodology for using PBPK/PD models in cumulative risk assessments.

C. Using hypothetical, simplified PBPK/PD models, explore the types of interactions that can occur among chemicals that effect an endpoint like cholinesterase inhibition, and develop recommendations about when default (e.g., relative potency factor) methodologies are likely to be inadequate.
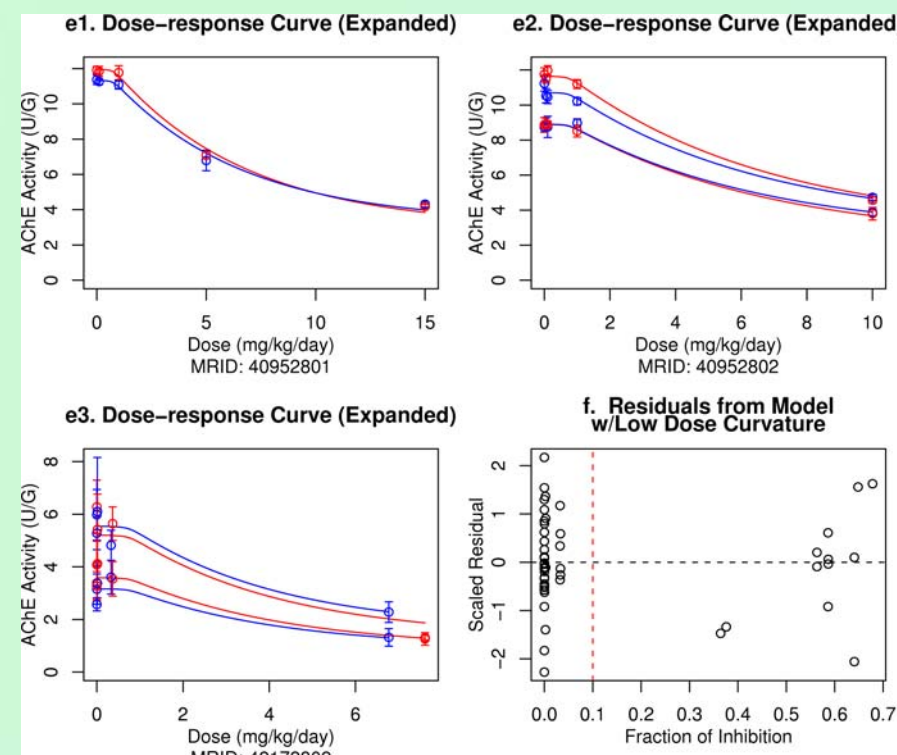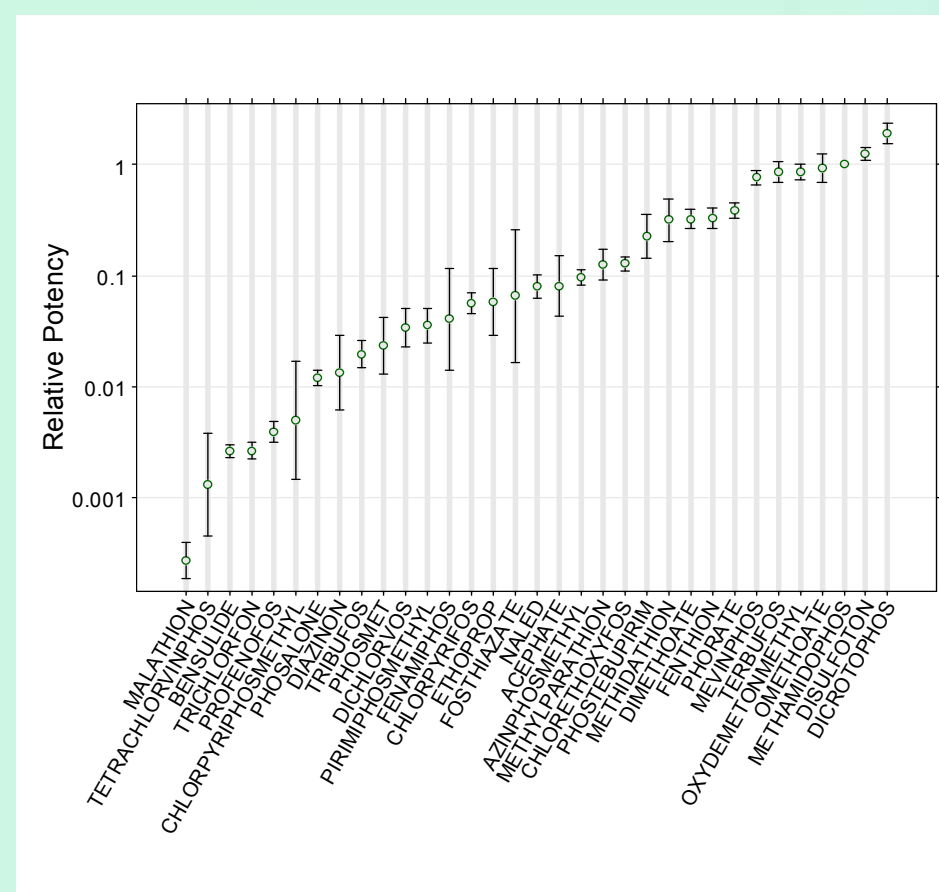

Dose-response curves for an example OP pesticide: chlorpyrifos from the OP CRA. There were three separate studies, two of which involved multiple time points.
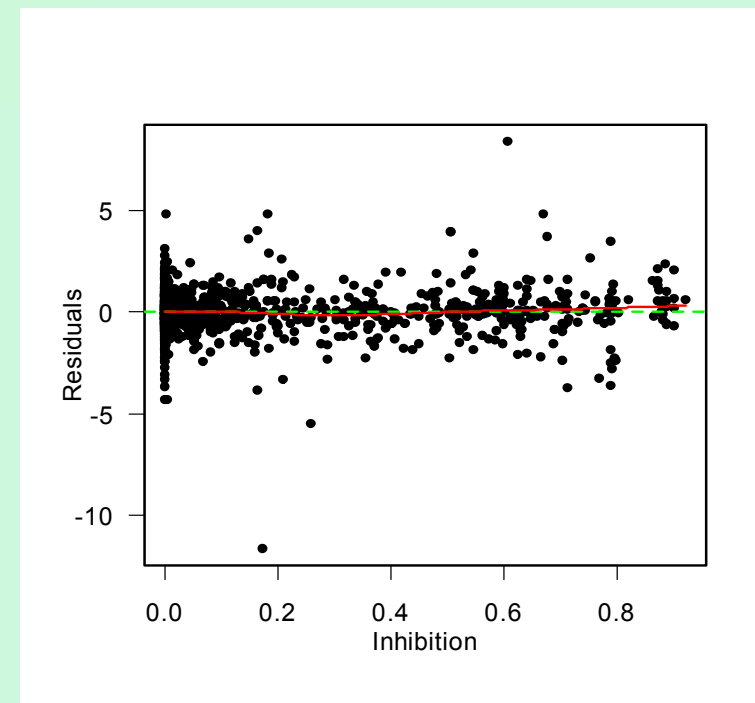

Residuals from model fits to all the data sets for all OPs, plotted against expected fraction inhibition. The uniform distribution about 0 over the entire range of inhibition testifies to the correctness of the model used.

Final Relative Potency Factors and 95% confidence intervals (note the log scale on the RPF axis).

- OPs inhibit acetylcholine esterase (AChE) irreversibly.

- The Cumulative Risk Assessment for the OPs was carried out by EPA's Office of Pesticide Programs and is based on relative potency factors (RPFs) — the goal of the dose-response modeling is to calculate RPFs and the benchmark dose (BMD) for the index chemical, methamidophos in this Assessment.

- RPF for the target chemical is the BMD_{10} for the index chemical (dose yielding 10% brain AChE inhibition) divided by the BMD_{10} of the target chemical.

- Risk assessment based on using RPFs to convert exposure to multple OPs to the equivalent exposure to the index chemical, and computing margins of exposure relative to the BMD_{10} for the index chemical.

- There were multiple dose-response datasets available for most chemicals.

- The dose-response model used was a combination of a simple PBPK-derived model to account for low-dose shape with an exponential model, modified to allow an asymptotic inhibition level < 100%.

- Using statistically appropriate methodology, parameters for this model were estimated using all the datasets for each chemical.

- The shapes of the dose-response curves varied among the OPs: strictly speaking the RPF approach is not valid when this happens, though it is likely to be a reasonable approximation.

- This work is complete, and has been reviewed twice by the FIFRA Science Advisory Panel. The current CRA for the OPs uses these RPFs.

B. Dose-Response Modeling for the N-Methyl Carbamate Cumulative Risk Assessment
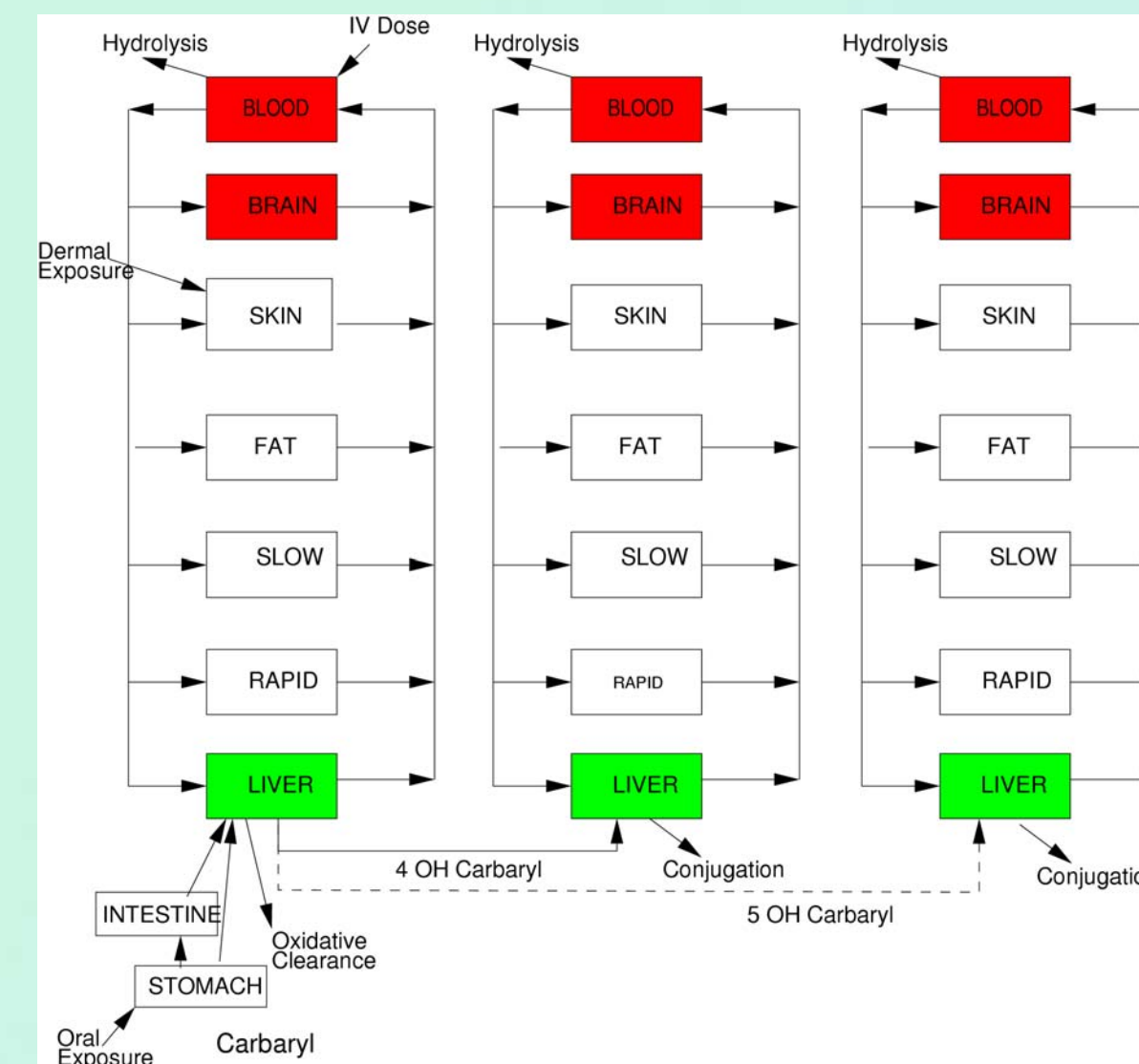

Proposed structure for PBPK/PD model for carbaryl and two active metabolites. Exposure can occur through oral or dermal pathways. Models for exposures to mixtures are constructed by "stacking" single chemical models. Interactions can occur at metabolic steps (in compartments colored green), largely through competition, and at the point of AChE inhibition (compartments colored red).

- N-methyl carbamates inhibit AChE reversibly, so the time component of exposure is relatively more important than it was with OPs.

- Empirical dose-response models (similar to those for the OPs), will be constructed, and a conventional RPF-based assessment will be done as part of the N-methyl carbamate cumulative risk assessment with OPP.

- PBPK/PD models are also being developed for this class of pesticides to relate projected exposures to n-methyl carbamates in food, water, and through residential use to AChE inhibition. Such models will allow the temporal dimension of the toxicity, due to the relatively rapid reversibility of AChE inhibition to be explicitly incorporated in the risk assessment.

- The goal is to be able to predict any potential interaction among n-methyl carbamates through processes such as competition for activating or clearance pathways, and competition for AChE, processes that can be parameterized, in principle, through understanding single chemical kinetics.
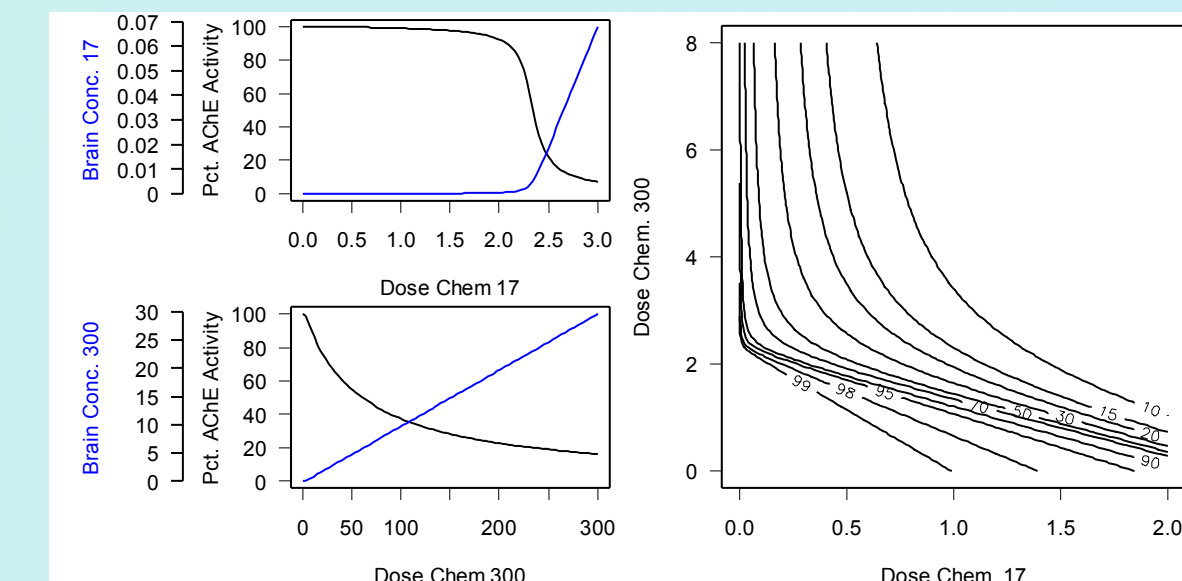
C. Theoretical Approaches to Cumulative Risk Methodology
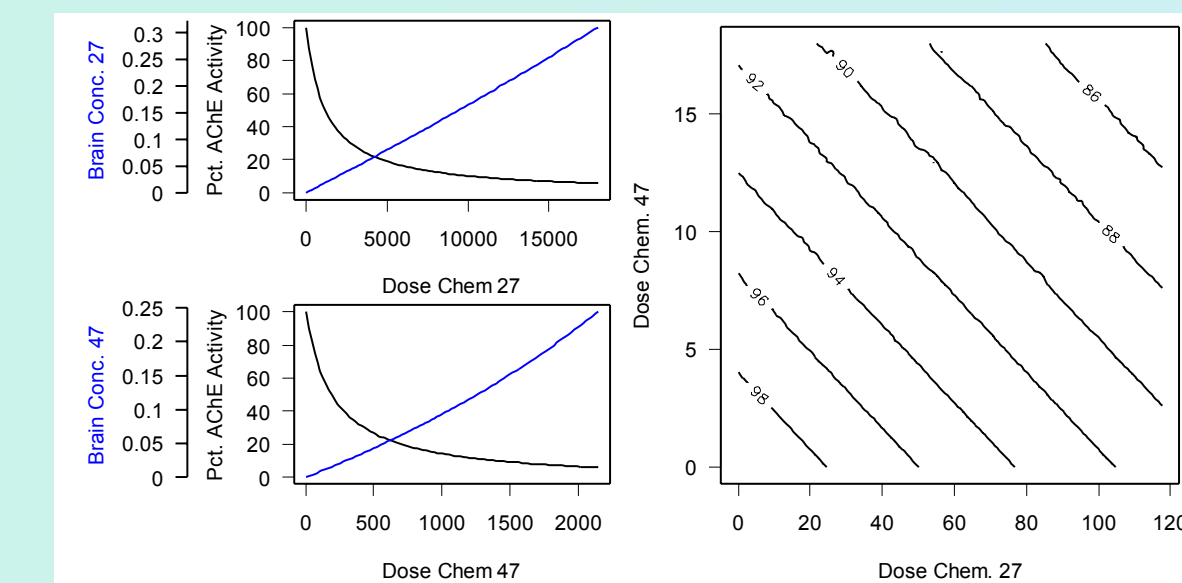
Dose-response curves and isobologram for two hypothetical OP-like AChE inhibitors. Dose-response curves are similar, and isoboles (curves connecting combinations of doses that result in the same level of AChE inhibition) are linear and parallel. Relative Potency Factors would accurately describe the effects of joint exposure to these two compounds.
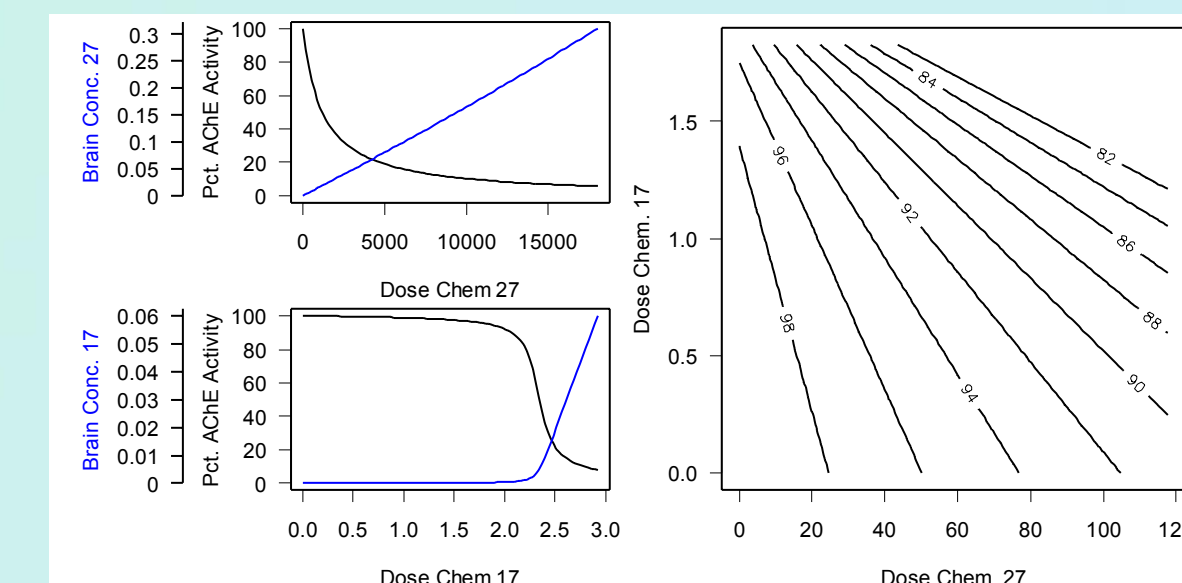
In this example, the shapes of the two curves are quite different. Isoboles are still linear, but now are not parallel. RPFs are strictly inappropriate, but their error needs to be evaluated. Perhaps basing RPFs on a lower response rate would improve the approximation. This can be evaluated computationally. Alternatively, the fact that isoboles are linear can be used to construct an alternative to RPFs.

Three examples of interactions among hypothetical chemicals. The examples were generated by a three compartment PBPK model. Each chemical inhibits AChE, and is cleared by the same metabolic pathway active in the liver.

Finally, in this example, the only difference between Chem 17 and Chem 300 is that the Ki (bimolecular inhibition constant) for Chem 17 is 10^4 time that for Chem 300. The interaction is probably due to competition at the point of metabolic clearance. In this case, only the PBPK/PD model, but not simpler approaches based on empirical dose-response models, predicts the inhibition due to a joint exposure.

- Conventional wisdom has it that, if chemicals act through a "common mode of action" then their combined toxicities should be predicted by relative potencies.

- Both simplified (toy) and more realistic models for the toxicity of classes of compounds are useful for exploring the conventional wisdom, and for developing/exploring other approaches to cumulative risk assessment, short of full PBPK/PD modeling.

- This study will use both toy and realistic models of OP- and carbamate-like compounds that inhibit AChE to investigate:

  - Determinants of dose-response shape

  - Consequences for chemical-chemical interactions of different PBPK structures

  - Approaches to using information from empirical dose-response in cumulative risk assessments.